Modelling firing pattern transitions in rat SON MNCs subject to osmotic stress

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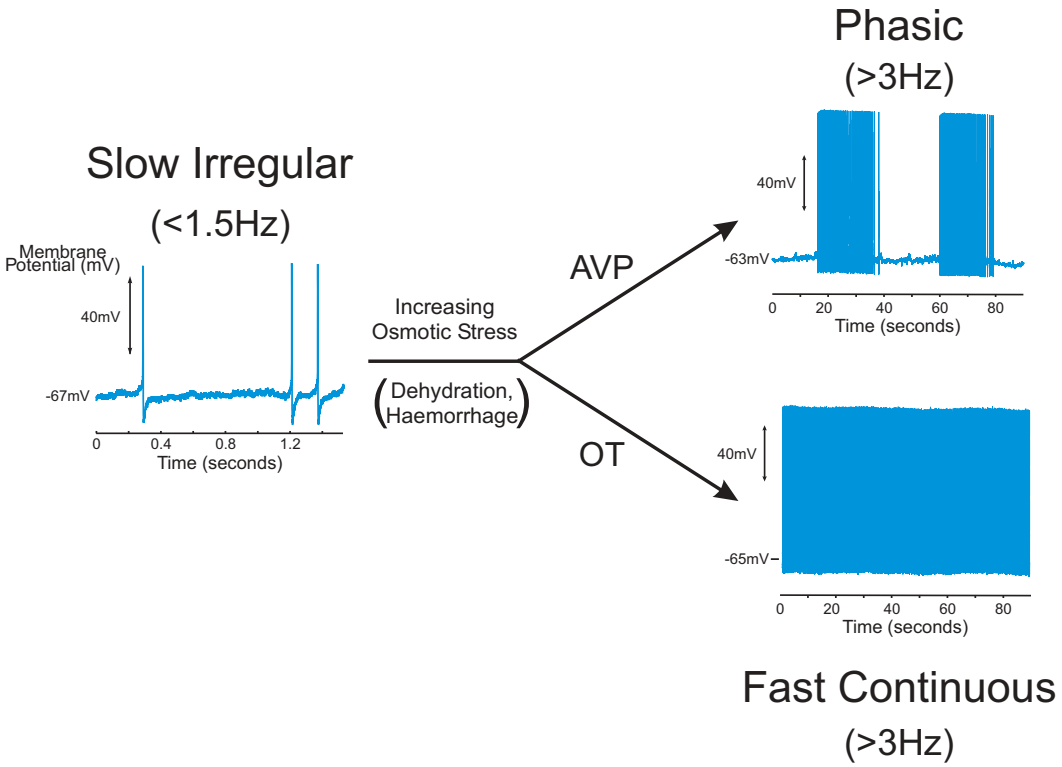
Introduction

The hormones arginine vasopressin (AVP) and oxytocin are secreted by magnocellular neurosecretory cells (MNCs) of the supraoptic and paraventricular nuclei. These hypothalamic neurons project to the pituitary and secrete their hormone directly into the blood whenever an action potential arrives at the nerve terminal.



Both hormones control osmolality and blood pressure, and their basal secretions are mediated by a slow (<1.5Hz), random firing pattern – a *slow-irregular discharge*. Increased peptide secretion is necessary during dehydration and haemorrhage, however the two cell-types show different electrical responses to the progressive stimulus – OT cells start to fire a *fast-continuous* (> 3Hz) pattern, while AVP cells move to a *phasic pattern* (mean frequency > 3Hz). These transitions are physiologically relevant and are readily seen *in vivo* after several hours dehydration.

Mathematical Model

OT:

$$\frac{\mathrm{d}}{\mathrm{d}t}V \;=\; -\frac{1}{C}(I_{spike} + I_{AHP} + I_{SOR} + I_{Ca} + I_{leak} + I_{osm} + I_{syn})$$

AVP:

$$\frac{\mathrm{d}}{\mathrm{d}t}V \;=\; -\frac{1}{C}(I_{spike} + I_{AHP} + I_{Ca} + I_{Na,leak} + I_{K,leak} + I_{osm} + I_{syn})$$

where $I_{spike} \equiv I_{Na} + I_K + I_A + I_c$

Simple calcium dynamics:

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{Ca}^{2+}]_i \;=\; \alpha I_{Ca}(t) - \frac{1}{\tau_{Ca}}\left([\mathrm{Ca}^{2+}]_i - [\mathrm{Ca}^{2+}]_{rest}\right)$$

Osmotic stress depolarizes the cell *via* several mechanisms:

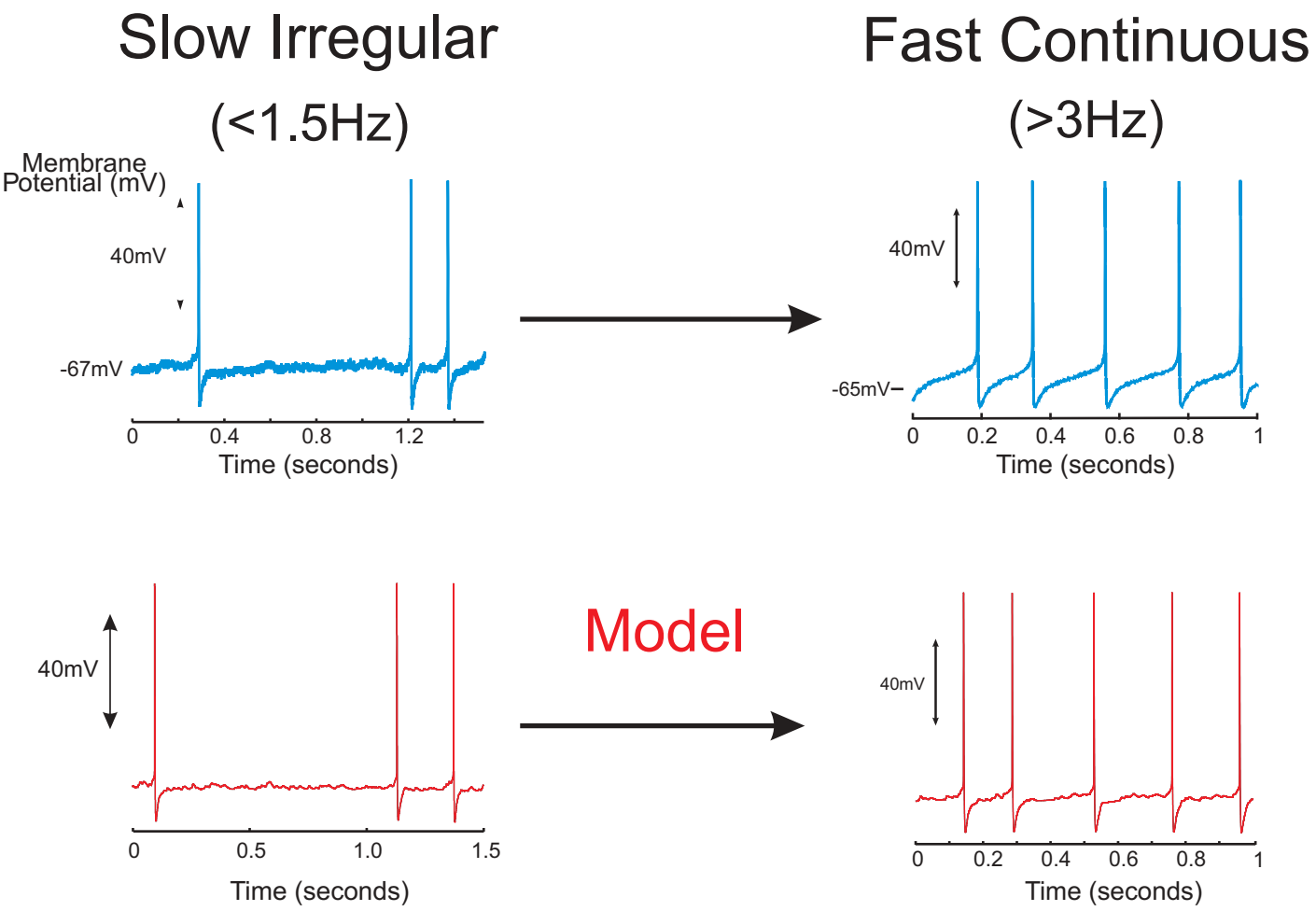
- an increase in excitatory synaptic input
- activation of non-specific cation channels;
- upregulation of persistent sodium channels;
- osmo-dependent regulation of taurine secretion.

We model the sum of these effects with a constant current – I_{osm}.

OT cell Transitions

Slow-Irregular* $\Rightarrow$ *Fast-Continuous

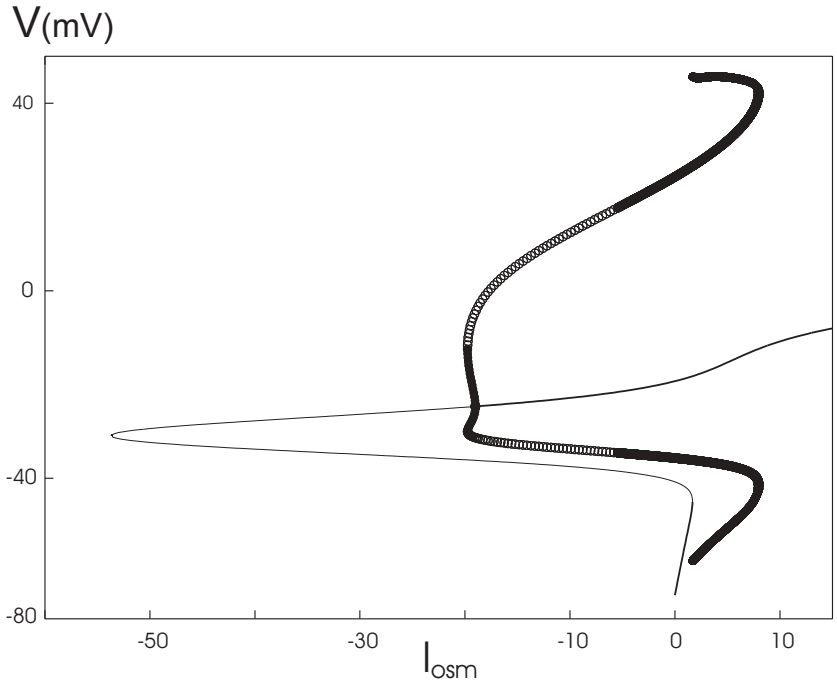
As osmotic stress is progressively increased, OT cells pass from a *slow-irregular* to a *fast-continuous* pattern.



Analysis of OT model

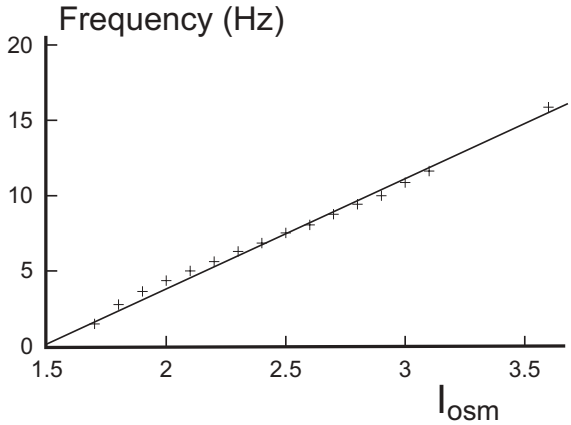
Effect of osmotic stress

As I_{osm} increases from zero, the model displays a saddle node bifurcation.



- Below the bifurcation the model is sub-threshold and spikes can only be evoked by depolarizing events (*e.g.* EPSP's)
- Above the bifurcation the cell fires repetitively

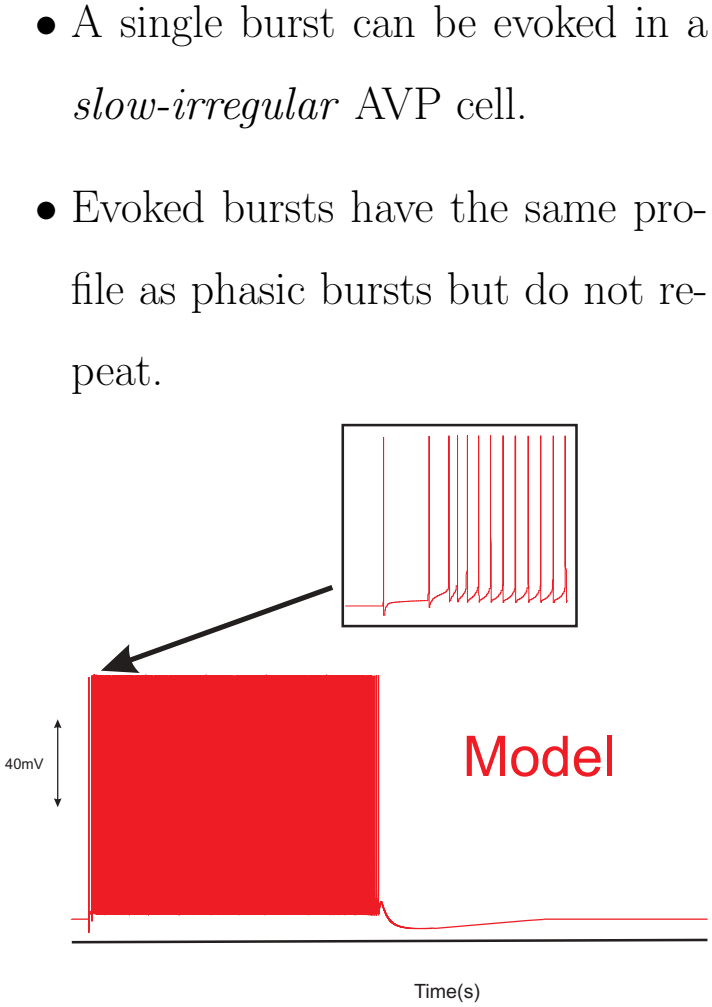
The firing rate increases linearly with with I_{osm}, and is linearized by the adaptive currents I_{SOR} and I_{AHP}. A linear firing rate increase is also seen *in vivo* and *in vitro* .

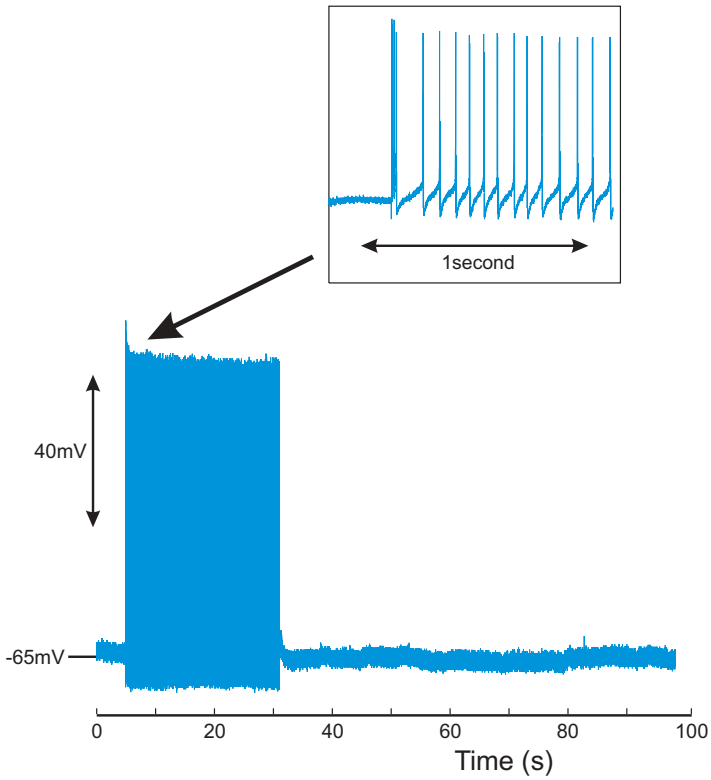


AVP cell Transitions

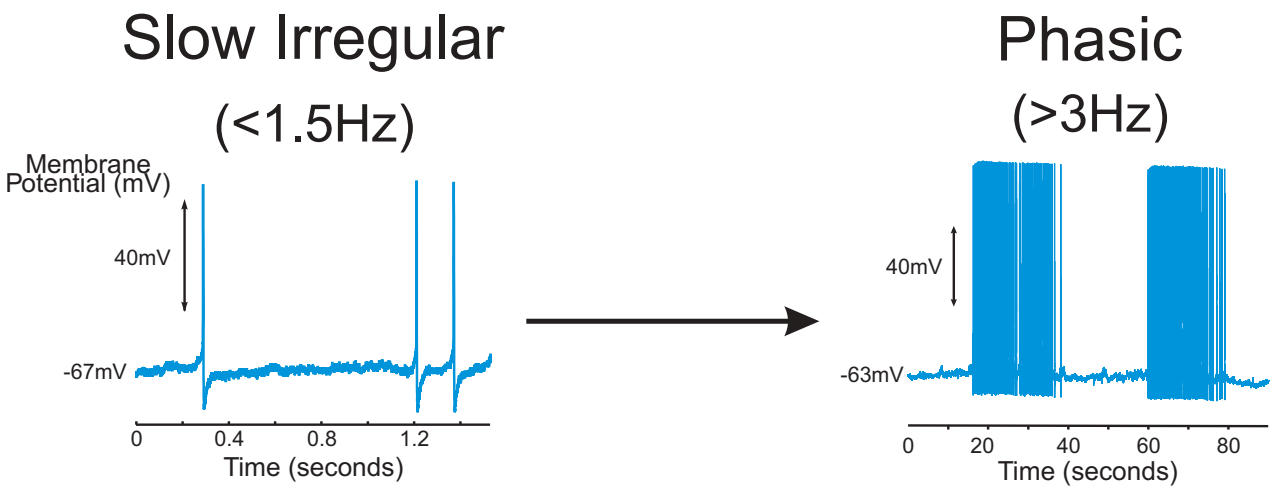
Slow-Irregular* ⇒ *Phasic

- A single burst can be evoked in a *slow-irregular* AVP cell.
- Evoked bursts have the same profile as phasic bursts but do not repeat.



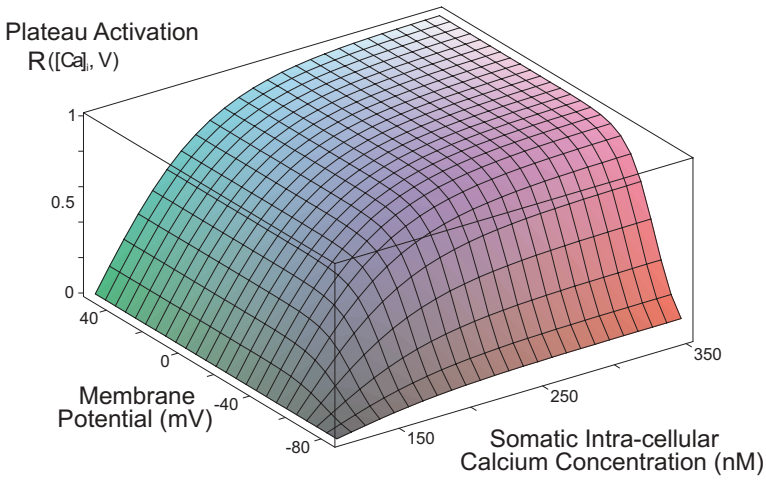


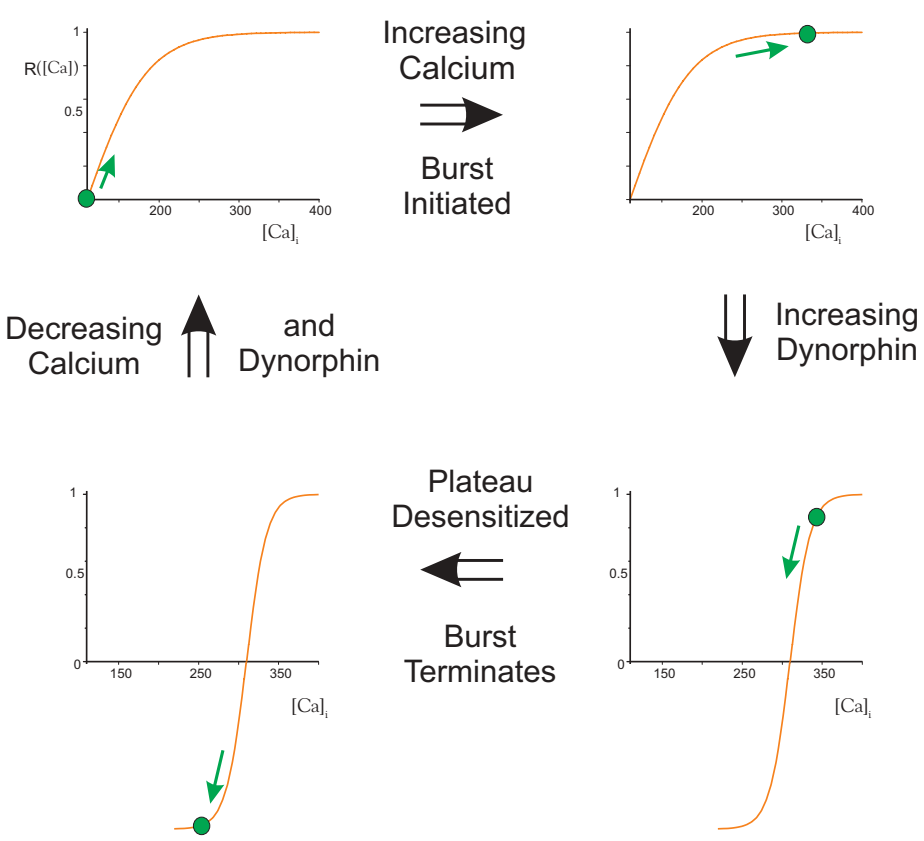
As osmotic stress is progressively increased, AVP cells pass from a *slow-irregular* to a *phasic* pattern of repeating bursts.



AVP cell Bursting Mechanism

Burst rides upon a plateau potential, which is sustained by the Ca^{2+}-mediated inhibition of a resting K^+ current ($I_{K,leak}$).





- Burst terminates by the progressive desensitization to Ca^{2+} of $I_{K,leak}$.
- Mediated by an extracellular accumulation of the opioid dynorphin (D).
- System not bistable and so must have two slow variables.

Dynorphin equation:

$$\frac{\mathrm{d}}{\mathrm{d}t}D = \Delta_D I_{Ca} - \frac{D}{\tau_D} \quad \text{where} \quad \Delta_D = \alpha + \beta D$$

Analysis of AVP model

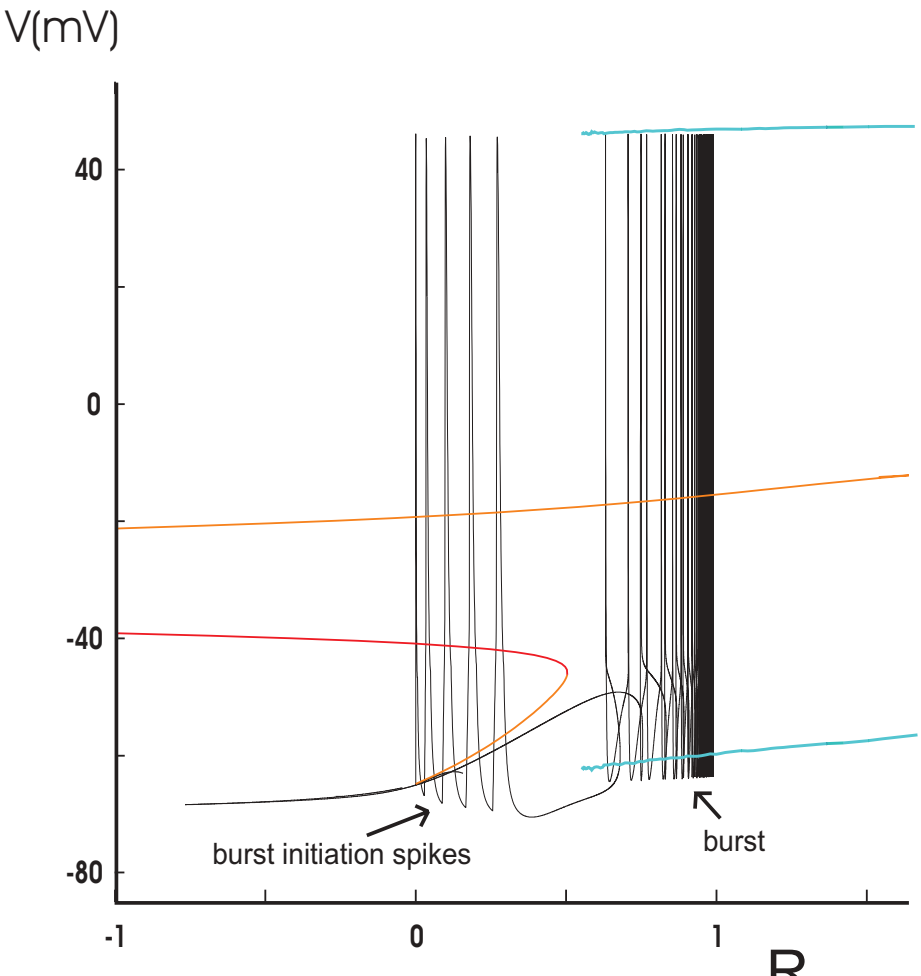
Fast-Slow reduction

Divide the model into two disconnected subsystems:

- a *fast* system (the spiking currents)
- a *slow* system (the Ca^{2+} /D oscillation and its effect on the plateau)

***Fast* subsystem:** Use R (activation of the plateau potential) as a bifurcation parameter. The *fast* system has a saddle node bifurcation (SNIC). The cell is silent when below the SNIC and fires repetitively when above it.

Slow oscillation moves the fast system back and forth through the bifurcation. Each slow oscillation corresponds to a single burst/silent period (*cf.* the Plant model).



Slow subsystem

- *Slow* subsystem strongly coupled to the *fast* subsystem since both Ca^{2+} influx and D accumulation are spike driven.
- Dissociation of subsystems is non-trivial.

Empirically, firing frequency is $f \propto \sqrt{R}$ for $R > 0.55$, and so we can separate the systems with this *ansatz*:

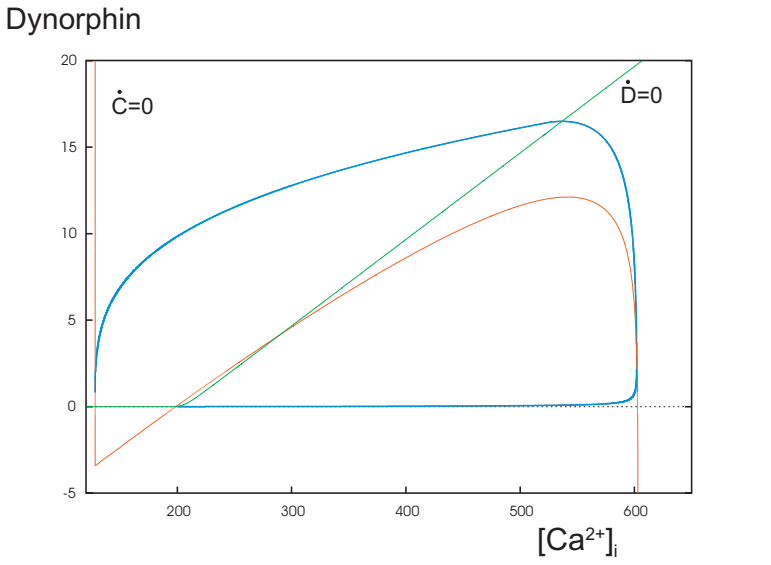
$$\begin{aligned} \frac{d}{dt}[\mathrm{Ca}^{2+}]_i &= f(R)\Delta_{Ca} - \frac{1}{\tau_{Ca}}\left([\mathrm{Ca}^{2+}]_i - [\mathrm{Ca}^{2+}]_{rest}\right) \\ \frac{d}{dt}D &= f(R)\Delta_D - \frac{D}{\tau_D} \end{aligned}$$

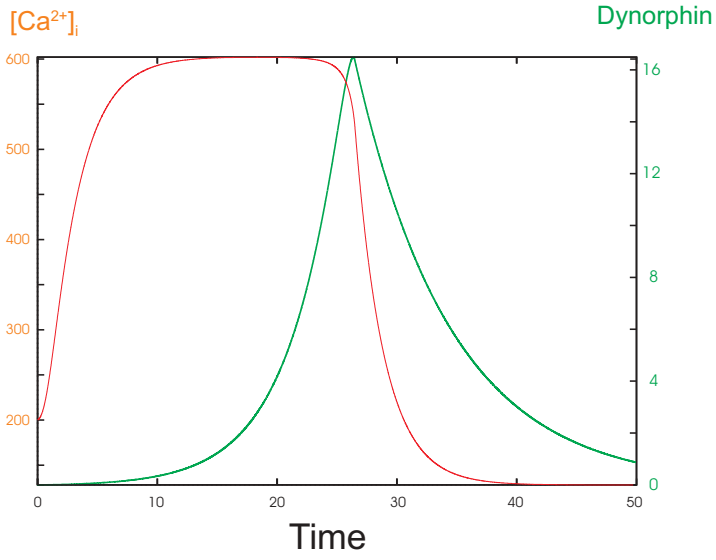
Further simplify by assuming R depends only upon Ca^{2+} and D and not V.

Phase Plane Analysis

Sub-threshold behaviour

- Stable fixed point at $D = 0$ and $[\mathrm{Ca}^{2+}]_i = [\mathrm{Ca}^{2+}]_{rest}$.
- System is excitable and single oscillations can be evoked by moving the system above threshold ($\Delta\mathrm{Ca}^{2+} > 30\mathrm{nM}$).



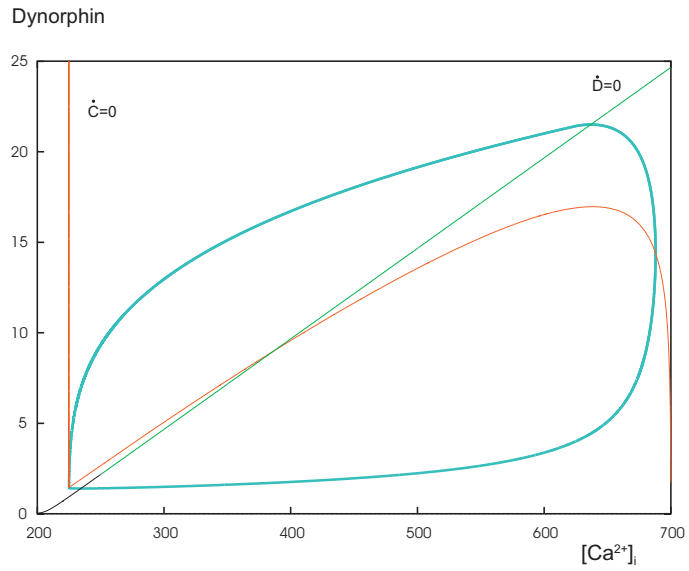


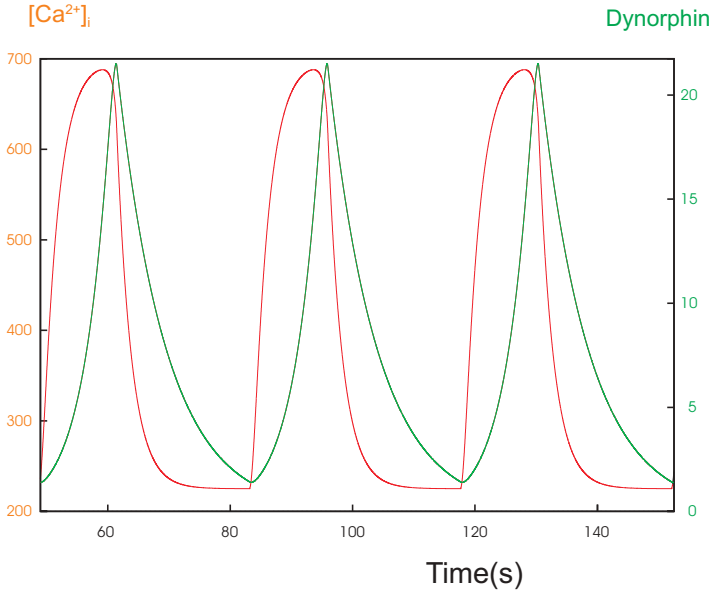
- Single oscillations are equivalent to evoked bursts in the full model.
- Threshold is close to the calcium influx due to 3 spikes.

Phase Plane Analysis

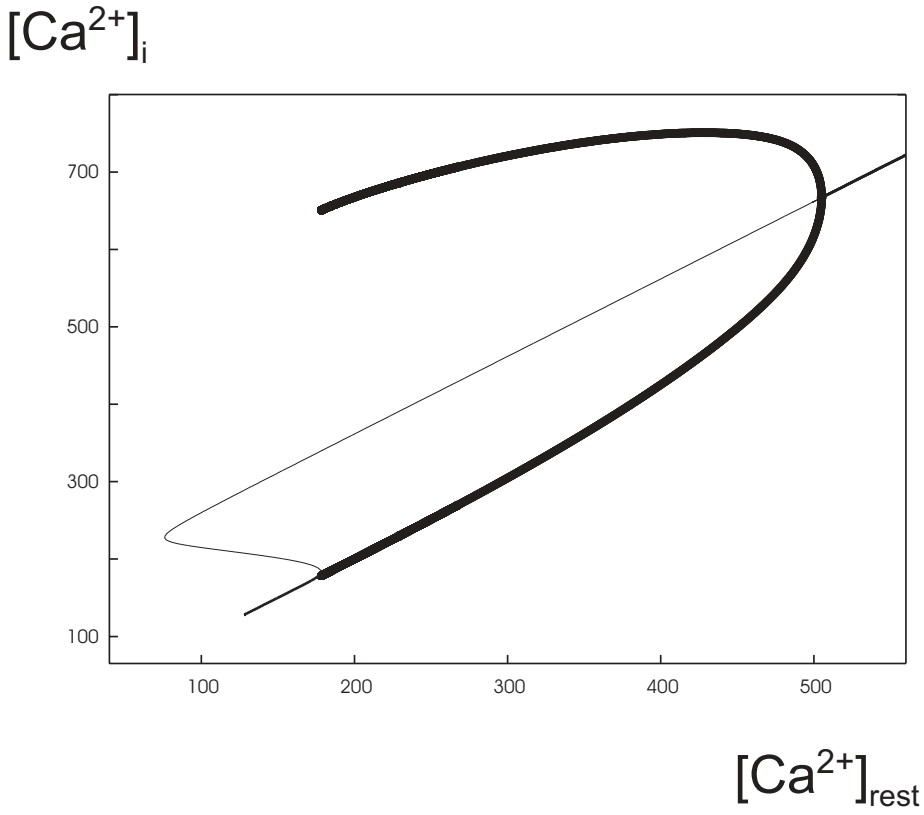
Super-threshold behaviour

If the resting calcium level ($[Ca^{2+}]_{rest}$) is increased above threshold, then the fixed point loses stability and the system starts to oscillate – the nascence of phasic activity.





Bifurcation Analysis



- Use $[Ca^{2+}]_{rest}$ as a bifurcation parameter.
- The *slow* subsystem passes through a saddle-node bifurcation and becomes oscillatory as $[Ca^{2+}]_{rest}$ increases.
- If $[Ca^{2+}]_{rest}$ increased further, *slow* system subsequently passes through a Hopf-bifurcation and the fixed point restabilizes.
- The resulting steady state is a plateau potential that does not oscillate, but is still above the threshold for the *fast* system to fire.
- Thus the complete system switches to a *fast-continuous* discharge pattern.
- This final transition has been seen under conditions of extreme dehydration (several days).

Conclusions

- We have presented a mathematical model that reproduces the transitions in firing seen in OT and AVP cells subject to progressive osmotic stress.
- The OT model exhibits a saddle node (SNIC) bifurcation, above which it fires regularly. Crossing the SNIC corresponds to the transition from *slow-irregular* to *fast-continuous* firing.
- The AVP model has a *fast system* that also has an SNIC bifurcation, and when osmotically stressed a *slow oscillation* carries the *fast system* above and below the SNIC – *phasic firing*.
- When subject to extreme osmotic stress the slow system passes through an Hopf bifurcation and the fixed point stabilizes. The slow system "locks up" and the cell starts to fire in a *fast-continuous* pattern.

Thanks and Acknowledgments

We would like to thank William Armstrong, Ryoichi Teruyama and Talen Shevchenko for advice and guidance, and R. Teruyama for allowing us to reproduce his data – all traces shown in blue.